Clinical Review

Acromegaly Update—Etiology, Diagnosis and Management

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Acromegaly is a disease with unique clinical manifestations. Its confirmatory diagnosis, however, requires basal and dynamic tests of growth hormone secretion. The measurement of circulating levels of somatomedin C has been a valuable addition to the diagnostic armamentarium. We review the etiology of acromegaly, with particular reference to the different histochemical and ultrastructural forms of somatotropic adenomas and their respective clinical behaviors. Ectopic sources of growth hormone-releasing hormone and of growth hormone itself are now well-recognized, though unusual, causes of acromegaly. The treatment of acromegaly is often problematic and far from uniformly successful. Initial enthusiasm for the results of surgical treatment has now been tempered by reports of increasing rates of recurrence on long-term follow-up. The roles of irradiation and pharmacotherapy are reviewed with particular emphasis on the use of bromocriptine, which has added a new dimension to the control of the somatic and metabolic manifestations of hypersomatotropism. Studies have been done recently using a long-acting somatostatin analog with encouraging results.

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Acromegaly, a syndrome of abnormal growth and proportion accompanied by metabolic derangements, was first described a century ago in 1886[1] by Marie and was the earliest pituitary disorder to be clinically recognized. Although autopsy studies documented the association of pituitary tumor with acromegaly,[2,3] not until 1909 did Bailey, Cushing and Davidoff confirm that anterior pituitary surgical intervention resulted in amelioration of some of the signs and symptoms of the disorder, thus further supporting the thesis that it was a syndrome of pituitary hyperfunction.[4] In a series of elegant animal experiments using injections of anterior pituitary extracts, Evans and Long[5] were able to produce features of gigantism in rats.

Physiology of Growth Hormone Secretion and Action

Growth hormone (Table 1) is a 191-amino acid polypeptide that is the predominant secretory product of the anterior pituitary.[6] Growth hormone secretion is under the dual control of hypothalamic stimulation and inhibition. Growth hormone-releasing hormone (GHRH) stimulates growth hormone secretion,[7,8] while somatostatin inhibits its secretion.[9] Peripheral hormones, such as estrogens, hydrocortisone and triiodothyronine, also appear to modulate the synthesis and secretion of pituitary growth hormone. Estrogens have been shown to enhance growth hormone secretion. Indeed, premenopausal women have greater growth hormone concentrations and secretory rates than normal men, whereas growth hormone levels in postmenopausal women are comparable to those in men.[10] Premenopausal women exhibit greater growth hormone responses to arginine than do men, but these responses in men can be made comparable to those of premenopausal women by pretreating with estrogens.[11] The implications of the increase in growth hormone secretion in women of reproductive age are attenuated by the fact that estrogens appear to inhibit production of somatomedin C.[12] Long- and short-term glucocorticoid excess results in suppression of growth hormone secretion,[10] which may play a role in determining the growth retardation of children with chronic glucocorticoid excess. Hypothyroid children have blunted growth hormone responses to insulin-induced hypoglycemia and GHRH,[13] and this may be relevant to the growth disturbance of thyroid hormone deficiency.

The growth-promoting effects of growth hormone are be-

TABLE 1.—*Nomenclature of the Hypothalamic-Pituitary Growth Hormone*

Hormone	*Source*	*Action*
Growth hormone-releasing hormone	Hypothalamus	Stimulates growth hormone secretion
Somatostatin	Hypothalamus	Inhibits growth hormone secretion
Growth hormone	Pituitary (somatotrope cell)	Stimulates somatomedin C; antagonizes insulin action
Somatomedin C	Liver; other tissues	Stimulates bone growth; stimulates cell replication

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ABBREVIATIONS USED IN TEXT

ACTH = adrenocorticotropic hormone
CT = computed tomography
GHRH = growth hormone-releasing hormone
IGF-I = insulinlike growth factor I
TRH = thyrotropin-releasing hormone
TSH = thyroid-stimulating hormone

lieved to be mediated through the action of somatomedin C/insulinlike growth factor I (IGF-I).[14] Growth hormone stimulates the production of IGF-I in the liver, which is probably the major source of circulating IGF-I levels.[15] IGF-I, however, is also produced in most if not all other tissues, and such tissue production is responsive to growth hormone.[16] It is not clear whether the bioactivity of IGF-I is dependent on the circulating peptide (endocrine action) or if IGF-I is predominantly acting at or close to its site of synthesis on neighboring cells (paracrine action) or on the same cell that synthesized it (autocrine action). The complexity of these interactions is heightened by the fact that other somatomedins distinct from IGF-I and their binding proteins are also produced in various tissues, and they are variously regulated by growth hormone.[17] In addition, growth hormone has further direct peripheral actions in inhibiting the action of insulin on carbohydrate and lipid metabolism.[17-19] IGF-I has also recently been shown to act via a classic negative feedback loop in suppressing basal- and GHRH-stimulated gene expression and secretion of pituitary growth hormone.[20,21] IGF-I may also regulate hypothalamic somatostatin secretion.[20]

Etiology

The clinical features of acromegaly all result directly or indirectly from a sustained hypersecretion of growth hormone.[22] In recent years, the availability of specific hormone radioimmunoassays, computed tomographic (CT) scanning and sensitive immunohistologic techniques have resulted in the elucidation of several causes of acromegaly (Table 2).

Pituitary Causes of Acromegaly

The growth hormone-secreting cells (somatotropes) comprise about 50% of the cells of the anterior pituitary gland and are readily identified by sensitive and precise immunocytochemical and electron-microscopic techniques.[23] It is from these cells that growth hormone-secreting adenomas arise. The formation of a somatotropinoma (growth hormone-cell adenoma) probably accounts for more than 90% of the cases of acromegaly.[24] The pure growth hormone-secreting adenoma may either be densely granulated[25-38] with growth hormone-containing granules as seen on electron microscopy or sparsely granulated.[25,28,31,34,35,39-42] The former tumors contain large amounts of stored hormone and are usually slow growing, leading to an insidious clinical progression, often over many years. The sparsely granulated growth hormone-cell adenomas, however, are rapidly growing, locally invasive and often associated with suprasellar extension at clinical presentation. About 25% of all of these adenomas are bimorphous (combination of two cell types), which are classified as mixed growth hormone-cell and prolactin-cell adenomas.[41,43-48] About 10% of all somatotropinomas are derived from the acidophil stem cell.[26,49-51] These monomorphous (single cell type) growth hormone- and prolactin-containing tumors usually present with primary clinical features of hyperprolactinemia (galactorrhea, amenorrhea, impotence) and relatively mild acromegaly.

Mammosomatotropic monomorphous cell adenomas[52] are slowly growing growth hormone- and prolactin-containing benign tumors believed to be the mature variants of the acidophil stem cell adenomas. The patients clinically have acromegaly and high circulating growth hormone levels with normal to moderately raised prolactin levels.

Plurihormonal adenomas express growth hormone with prolactin, thyroid-stimulating hormone (TSH) or adrenocorticotropic hormone (ACTH).[28,53-55]

The natural history of acromegaly is highly variable, and the response of inappropriate growth hormone secretion to various stimuli and inhibitors in this condition is far from uniform. The ultimate relevance of this immunohistochemical classification would be enhanced if further correlations could be found between tumor cell types, dynamic growth hormone testing, such as to GHRH, thyrotropin-releasing hormone (TRH), dopamine agonists and glucose, and response to therapy, such as radiosensitivity or bromocriptine-responsiveness.

Most of the extrapituitary causes of acromegaly have only recently been fully documented and their pathogenesis clarified.

Aberrant somatotropic cell adenomas. These adenomas arise in pituitary tissue remnants in the sphenoid or parapharyngeal sinuses,[56-58] reflecting the embryologic origin of the anterior pituitary from Rathke's pouch.

Extrapituitary Causes of Acromegaly

Ectopic growth hormone-secreting tumors. The existence of extrapituitary growth hormone was suggested by the in vitro finding of immunoreactive growth hormone in lung adenocarcinoma,[59] breast cancer[60] and ovarian tissue extracts.[60] Recently a patient harboring a growth hormone-secreting intramesenteric islet cell tumor with acromegaly was cured after excision of the abdominal tumor, which was shown to express growth hormone messenger RNA.[61] Based on the features of this so-far-unique case, patients with ectopic growth hormone

TABLE 2.—*Etiology of Hypersomatotropism**

Pituitary
Eutopic
Densely granulated growth hormone-cell adenoma
Sparsely granulated growth hormone-cell adenoma
Mixed growth hormone-cell and prolactin-cell adenoma
Mammosomatotrope-cell adenoma
Acidophil stem cell adenoma
Plurihormonal adenoma
Ectopic
Aberrant growth hormone-cell adenoma
Sphenoid sinus
Parapharyngeal sinuses
Extrapituitary
Ectopic growth hormone-secreting tumor
Pancreas
Excess GHRH secretion
Eutopic—hypothalamic hamartoma
Ectopic—pancreatic islet cell tumors; bronchial and intestinal carcinoid
Acromegaloidism

GHRH = growth hormone-releasing hormone

*Adopted from Melmed et al.[22]

secretion would be expected to have normal pituitary CT scans, no response of circulating growth hormone to TRH stimulation and undetectable levels of plasma GHRH.

Excess GHRH secretion: Eutopic: Hypothalamic hamartomas,[62] choristomas,[63] gliomas and gangliocytomas[64] may cause acromegaly. These tumors elaborate GHRH, causing acromegaly associated with excessive growth hormone secretion.

Ectopic GHRH secretion: Ectopic GHRH secretion has been documented in patients harboring pancreatic islet cell tumors[65-69] and lung and intestinal carcinoid tumors.[70-74] These patients present with the clinical features of classic acromegaly, accompanied by elevated circulating growth hormone and GHRH levels. Patients also often show mass effects (usually pulmonary) from their extrapituitary tumors, obvious metastatic disease or other humoral effects, such as insulin-induced hypoglycemia or carcinoid syndrome. The structure of GHRH was originally elucidated from extracts of pancreatic islet cell tumors removed from patients with this syndrome.[66,67,69] Following surgical removal of the tumors, growth hormone levels fell rapidly and clinical signs of acromegaly regressed. In some of these cases, examination of the pituitary showed evidence of growth hormone-cell (somatotrope) hyperplasia with a preserved reticulin network,[65,75] indicating the absence of an adenoma, wherein the reticulin network appears distorted.

The relative rarity of this condition was recently documented in a retrospective multicenter study of 177 unselected acromegalic patients where no cases of elevated circulating GHRH levels were found in previously undiagnosed cases.[76]

Acromegaloidism. Acromegaloidism, indistinguishable clinically from acromegaly, has been diagnosed in rare cases in patients with normal basal and dynamic growth hormone levels and no demonstrable pituitary or abdominal tumor. These patients may elaborate a unique growth factor distinct from growth hormone or somatomedin C.[77]

Clinical Features of Acromegaly

The classic physical features of acromegaly have intrigued physicians since the first description of the disorder (Table 3).

The clinical signs and symptoms of acromegaly are due to the effects of the local tumor mass in the pituitary, the peripheral effects of excessive growth hormone secretion and the endocrine effects of the disordered secretion of the other pituitary hormones.

Local Tumor Effects

In slow-growing tumors, the local features are usually not prominent. In the more aggressive tumors (usually seen in younger patients) these signs may be the presenting features.

Pituitary tumors enlarge and this may cause headache, visual field defects because of pressure on the optic chiasm or optic nerves or cranial nerve palsies.[78] Inferior expansion may erode into the sphenoid sinus. In rare cases these tumors may extend to the tips of the temporal lobe and may even cause uncinate seizures.[79] As the frequency of the early diagnosis of acromegaly increases, the prevalence of these local complications will decrease.

Patients with extrapituitary acromegaly will harbor either an abdominal or chest mass and may present with systemic features of carcinoid syndrome or even occasionally hypoglycemia from an islet cell tumor.

Effects of Excessive Growth Hormone Secretion

The earliest effects of excessive exposure to elevated growth hormone levels are coarsening of facial features with soft tissue swelling of the face, hands and feet.[80,81] This may occur insidiously, and the diagnosis is often confirmed by comparing serial photographs of patients taken over many years. Increased soft tissue volume results in patients noticing a progressively larger shoe size and ring diameter. These features depend both on the duration of the growth hormone hypersecretion and the degree of elevation of growth hormone levels. It appears that most of the somatic effects are mediated by excessive IGF-I levels,[16] whereas many of the metabolic effects, such as carbohydrate intolerance, are direct effects of growth hormone itself.[17-19] The prevalence of these clinical signs does not appear to differ substantially from the original description by Davidoff in 1926.[4]

As patients with acromegaly live longer, however, additional clinical features have become apparent. It appears that there is an association of colonic polyps in acromegalic patients who have skin tags.[82] Recently the association of colonic cancer and acromegaly has also been described, and this has confirmed the increased prevalence of cancer in cases of acromegaly.[82,83]

Other Endocrine and Metabolic Abnormalities

Acromegaly is associated with a multitude of metabolic abnormalities. The effects on carbohydrate and lipid metabo-

TABLE 3.—*Acromegaly—Clinical and Metabolic Features*

Local	
Visual field defects; cranial nerve palsy; headache	
Abdominal or chest mass	
Somatic	
Acral enlargement	Increased heel pad thickness; prognathism; hypertrophy of frontal bones; malocclusion; macroglossia
Musculoskeletal	Arthralgias; hypertrophic arthropathy; carpal tunnel syndrome; acroparesthesias; proximal myopathy
Skin	Hyperhydrosis; skin tags; acanthosis nigricans
Colon	Polyposis; carcinoma
Cardiovascular	Left ventricular hypertrophy; asymmetric septal hypertrophy; hypertension; congestive heart failure; arrhythmias; myocardial infarction
Sleep disturbances	Sleep apnea; narcolepsy
Visceromegaly	Salivary glands; liver; spleen; kidney
Metabolic and Endocrine	
Carbohydrate	Insulin resistance and hyperinsulinemia; impaired glucose tolerance; diabetes mellitus
Lipids	Hypertriglyceridemia
Mineral	Hypercalciuria; increased 1,25-dihydroxyvitamin D_3; increased urinary hydroxyproline
Electrolyte	Low renin; increased aldosterone
Gonadal	Menstrual abnormalities; galactorrhea; decreased libido; impotence; low testosterone-binding globulin
Thyroid	Thyromegaly; hyperthyroidism; low thyroid-binding globulin
Multiple endocrine neoplasia (I)	Hyperparathyroidism; pancreatic islet cell tumors

lism are probably due to a direct anti-insulin effect of growth hormone.[17-19] Curiously, despite hyperinsulinemia and clinically evident diabetes mellitus, the microvascular complications of diabetes seldom develop in persons with acromegaly. Reproductive disorders such as menstrual disturbances or galactorrhea in women and loss of libido and impotence in men are due to several factors, including associated hyperprolactinemia,[24,84] low testosterone-binding globulin levels and hypopituitarism with hypogonadotropinemia in patients with large pituitary tumors.[85] An increased prevalence of diffuse or nodular goiters is well recognized.[86] The interpretation of thyroid function tests may be complicated by a low thyroid-binding globulin level and an increased thyroid-binding prealbumin concentration.[86,87] ACTH and TSH deficiencies occur late in the natural history of the disease and require replacement therapy with hydrocortisone and thyroxine.

About 30% of patients with acromegaly have hyperprolactinemia. Elevated prolactin levels may be caused by a mixed somatotrope-lactotrope adenoma, production of growth hormone and prolactin from a single-cell-type tumor such as mammosomatotropic or acidophil stem cell tumor or, finally, by a plurihormonal adenoma consisting of two separate adenomas.[24] In larger, pure growth hormone-cell macroadenomas, pituitary stalk compression may also lead to hyperprolactinemia.

Hypercalcemia with abnormal calcium metabolism may occur in 3% to 16% of cases.[88] In a small proportion of these, this may be due to associated hyperparathyroidism as part of a syndrome of multiple endocrine adenomatosis (type I). In a review of 88 patients with this syndrome, 15 were found to have acromegaly.[89] Hypercalciuria is seen more commonly. In this regard, increased concentrations of 1,25-dihydroxyvitamin D_3 have been reported in patients with acromegaly, and these have been shown to decrease after treatment.[88] Increased 1,25-dihydroxyvitamin D_3 levels may play a role in the hypercalcemia and increased bone turnover occasionally encountered in this disease.[90]

Diagnosis of Acromegaly

The clinical diagnosis of acromegaly is usually clear-cut in long-standing cases, but may be subtle in the early stages of the disease. The diagnosis of acromegaly is based on strict biochemical criteria. Upper levels of normal for serum growth hormone in adults are 5 ng per ml in male patients and 10 ng per ml in female patients. The basal levels of growth hormone fluctuate physiologically,[91] however, and elevated levels are also found in patients who are stressed and in those with chronic renal failure, poorly controlled diabetes mellitus, malnutrition, anorexia nervosa and cirrhosis.[92] The finding of a single elevated serum growth hormone level is therefore not diagnostic of acromegaly. The absence of suppression of serum growth hormone levels (< 5 ng per ml in male patients and < 10 ng per ml in female patients) two hours after an oral glucose load (75 grams) establishes the diagnosis of pathologic hypersecretion of growth hormone in more than 90% of cases. About 20% of patients with acromegaly will in fact have a paradoxic elevation of growth hormone levels two hours after oral administration of glucose.[93-96] A stimulation of already elevated growth hormone levels after thyrotropin-releasing hormone administration is seen in about 75% of cases.[97] Clearly, therefore, a few patients with acromegaly, while manifesting the features of growth hormone excess, may have normal fasting growth hormone levels, normal growth hormone suppression after an oral glucose tolerance test and no stimulation of growth hormone after TRH administration.

The growth hormone dependency of IGF-I and its long half-life—in virtue of its almost complete binding to specific carrier proteins[98,99]—has aroused great interest in its value as a tool for diagnosis and follow-up of acromegaly. Several studies have pointed out that IGF-I levels appear to correlate better than fasting growth hormone levels or those after a one-hour glucose load with activity of the disease, such as heel-pad thickness.[100,101] IGF-I levels thus appear to represent a readily measurable assessment of growth hormone bioactivity. IGF-I levels can also increase in a number of physiologic conditions, such as puberty and late pregnancy,[102] and may be extremely low in persons with malnutrition.[103] The overlap, however, between normal persons and those with active acromegaly is small. Measuring IGF-I levels is appropriate as part of the initial diagnostic workup and the monitoring of the response to therapy in acromegaly. Several groups, however, have contended that neither growth hormone nor IGF-I levels alone correlate well with clinical responses following treatment of acromegaly.[104,105] Thus, somatomedin assays should supplement basal and dynamic tests for growth hormone for the endocrine diagnosis and follow-up of somatotropic adenomas.

Additional anterior pituitary function testing that provides useful information for postsurgical management includes measuring serum prolactin levels, doing thyroid function tests and assessing ACTH reserve.

Although plain lateral skull x-ray films reveal abnormalities of the sellar contour in 80% to 90% of cases,[106] the presence of microadenomas (less than 10 mm) is not detected by this method. High-resolution CT scanning is the best imaging technique currently available for the study of pituitary adenomas. While macroadenomas are often visualized as hyperlucent areas, microadenomas of up to 5 mm can be seen as hypodense or isodense intrapituitary lesions.[107] CT scanning has been disappointing in the study of the sellar anatomy following a pituitary operation or irradiation.[107] Suprasellar extension of adenomas or the presence of an empty sella, however, can be reliably detected by CT. Nuclear magnetic resonance imaging techniques have recently been introduced and show great promise. They show with precision the effects of the pituitary tumor mass on adjacent structures, particularly the visual pathway, and are better able to distinguish the intrasellar cerebrospinal fluid cistern of the "empty" sella from other lesions that present with a hypodense CT appearance such as fibrous, necrotic or cystic tissue.[108] There may still be an occasional role for angiographic techniques in persons harboring large pituitary masses in whom the relationship of the tumor to the neighboring blood vessels must be defined.[106]

The search for an extrapituitary cause of acromegaly through abdominal and chest CT scanning before therapy directed at the pituitary is probably not cost-effective when done on a routine basis as these are relatively rare conditions.[76] If there are symptoms pointing to an extrapituitary tumor, carcinoid syndrome or hyperinsulinemia; a normal pituitary CT scan with no response of growth hormone to TRH administration, or increased GHRH levels are encountered, then a CT search for an ectopic source of growth hormone or GHRH is indicated.

Therapy for Acromegaly

The aims of therapy for acromegaly are as follows:

- To treat the pituitary lesion, thus correcting or preventing local complications.
- To totally suppress disordered pituitary secretion of growth hormone, thus preventing progression of physical disfigurement and the metabolic or systemic effects of hypersomatotropinemia.
- To prevent or rectify other pituitary tropic hormone disorders.

Table 4 summarizes the criteria for the cure of acromegaly that have been used by several groups in recently published series. As will be discussed below, no single therapeutic option (Table 5) really offers a 100% successful cure of acromegaly. Medical or radiation therapy will often be required as adjuvants to surgical treatment. The development of newer pharmacological agents, especially somatostatin analogs, certainly holds much future promise.

Radiation Therapy

Conventional radiation therapy is used both as a primary and an adjuvant form of therapy in acromegaly.[114,115]

A total dose of 5,000 rads is administered over four to six weeks. The time required for this to effectively lower growth hormone levels by 50% is usually at least two years. The longer the time interval after irradiation, the greater the effectiveness of the treatment.[85,115-117] After ten years, normal growth hormone levels are seen in about 75% of persons with acromegaly. The arrest of tumor growth is almost uniformly seen, and most growth hormone-cell adenomas do shrink after irradiation.

Side effects. Radiation damage to the surrounding tissues may occur, especially if more than 5,000 rads are administered.[115-117] Hypopituitarism will develop in about 50% of patients after ten years. Hypocortisolism and hypogonadism are the usual tropic hormone deficits, while isolated hypothyroidism occurs in only about 10% of these patients. Mixed hypocortisolism and hypogonadism will develop in about 5% of patients.[115-117]

Proton beam therapy has also been used with considerable success in the treatment of acromegaly.[118] The advantage of this form of irradiation is that a patient can receive the total radiation dosage (4,500 to 6,500 rads) in only one or two visits without causing skin damage.

The slowness of the response seen with radiation therapy usually makes it an inappropriate option for young patients who may be alarmed by the prospect of progressive physical deformities. Furthermore, glucose intolerance and hypertension may be serious complications of acromegaly and clearly a rapid fall in circulating growth hormone levels would be desirable to prevent development or exacerbation of these complications.

TABLE 4.—*Criteria for Absolute Cure of Acromegaly*

Fasting AM growth hormone levels are less than 5 ng/ml in male patients and less than 10 ng/ml in female patients
Growth hormone secretion is suppressible after an oral glucose tolerance test*
Normal circadian rhythm of growth hormone secretion reappears†
Growth hormone levels increase normally after provocative stimulation‡§‖¶
IGF-I levels are normal#
Paradoxic growth hormone responses disappear†§‖

IGF-I = insulinlike growth factor I

*From Quabbe.[109]
†From Jaquet et al.[110]
‡From Faglia et al.[95]
§From Arafah et al.[111]
‖From Hoyte and Martin.[112]
¶From Pearson et al.[113]
#From Clemmons et al.[100]

TABLE 5.—*Treatment Options in Acromegaly*

Surgical
Transsphenoidal pituitary adenomectomy
Primary extrapituitary tumor resection
Radiation
Conventional supervoltage
Proton beam
Medical
Dopaminergic agonists (bromocriptine; pergolide mesylate)
Somatostatin analogs

Surgical Management—Transsphenoidal Surgery

The earliest cures of acromegaly were in fact described by Cushing in 1909, who used the transsphenoidal approach to surgically remove pituitary tumors.[119] Today, the most frequently used form of therapy in acromegaly is transsphenoidal pituitary adenomectomy done by a skilled and experienced neurosurgeon. A transfrontal pituitary operation is reserved for patients harboring large tumors with significant suprasellar extension or contiguity with blood vessels or optic nerves.[120,121]

The results of selectively resecting a growth hormone-cell adenoma are clear-cut and rapid. Growth hormone levels fall to normal within an hour of tumor excision, and the soft tissue and metabolic effects of elevated growth hormone levels are ameliorated almost immediately. The hard tissue changes induced by the acromegaly are, however, irreversible.

The following clinical and biochemical features will predict the success of surgical treatment[122,123]:

- Microadenoma is totally confined within the pituitary fossa.
- Random serum growth hormone levels are less than 40 ng per ml.

Patients fulfilling these two criteria will have an initial success rate of almost 90% as assessed by a reduction in serum growth hormone levels to less than 5 ng per ml.[122-126] Normal pituitary function is usually restored postoperatively if the tumor is well encapsulated. Despite these good results observed in most major centers, recent evidence has indicated that long-term results (five years and later) in these patients are not at all as favorable.[127] Tumor recurrence with or without clinical features of acromegaly and evidence of failure to suppress growth hormone levels after oral administration of glucose have been observed in patients who had initially been "cured." Further data from follow-up studies are required to allow a fuller evaluation of the long-term results of the transsphenoidal pituitary operation.

Side effects. Clearly the most important endocrine side effect of surgical treatment is damage to the remainder of the pituitary gland with resultant pituitary failure and the necessity for life-long hormone replacement.[95,109]

Surgical morbidity including cerebrospinal fluid leaks, sinusitis, central nervous system damage, hemorrhage, transient or permanent (infrequent) diabetes insipidus and bacterial or sterile meningitis occurs in about 5% of all patients. An empty sella syndrome postoperatively may in rare cases lead to visual impairment. The incidence of these complications depends on the size of the tumor.[122,123,125,126]

Finally, as with any major operation, about a 1% mortality rate exists. These operative deaths are usually only seen in patients with large invasive tumors.[121]

It should be emphasized that the recurrence of acromegaly after surgical treatment may indicate incomplete surgical resection of tumor tissue.[122] Although growth hormone-cell adenomas are usually well confined, functioning tumor cells may invade the dura and are thus difficult to visualize and resect.

Medical Treatment of Acromegaly

Bromocriptine. 2-Bromo-α-ergocriptine, a lysergic acid ergot derivative, has recently been approved by the Food and Drug Administration for use in the treatment of acromegaly. This dopamine agonist binds to pituitary dopamine receptors and will cause a substantial suppression of prolactin secretion in normal patients and those with prolactin-secreting adenomas. Because neoplastic somatotropes probably respond inappropriately to dopamine agonists by suppressing growth hormone secretion in more than 50% of persons with acromegaly,[128] bromocriptine is used as both a primary and an adjuvant medication for acromegaly.

The doses of bromocriptine used in acromegaly are usually higher than those required to suppress prolactin secretion. It is noteworthy, however, that if a beneficial effect of the use of bromocriptine is to be observed, it is usually seen with doses of as much as 20 mg bromocriptine a day.[129-132] Higher doses are usually unwarranted, as side effects of the drug will become more apparent. These include headache, nasal stuffiness, nausea, vomiting, transient postural hypotension, cold-induced peripheral vasospasm, depression, nightmares and hallucinations.[133] These side effects are usually reversible after decreasing the dose.

In more than 20 published series from Western Europe and the United States, it appears that basal serum growth hormone levels are decreased to less than 10 ng per ml in about 50% of cases (range 10% to 80%). A growth hormone level of less than 5 ng per ml has been found in 20% of reported cases (range 5% to 60%),[85] while shrinkage of tumor size probably only occurs in about 10% to 20% of cases in published series.[134,135] Interestingly, however, most patients (about 70%) noted a significant improvement in clinical well-being, including reduction of perspiration, decreased soft tissue swelling and decreased ring size.[136] There is controversy regarding the correlations between clinical responses to bromocriptine therapy and serum levels of growth hormone after oral glucose is given and IGF-I levels are measured. While some authors claim that growth hormone levels are a more faithful index of therapeutic response,[104,136,137] others[105] have found that IGF-I levels are superior in this respect. In fact, Wass and co-workers have described a subgroup with unchanged growth hormone levels but decreased IGF-I levels who had improved clinically and metabolically.[105] Thus it appears that bromocriptine may induce clinical improvement in many patients in spite of persistently raised growth hormone or IGF-I levels (or both). Some groups have reported that bromocriptine may selectively suppress the monomeric, biologically active form of growth hormone,[138] whereas immunoreactive growth hormone levels remain unchanged or only slightly decreased. Hizuka and associates and others, however, have found no differences in elution profiles of growth hormone on Sephadex G 100 chromatography or alterations in growth hormone-binding properties in patients receiving bromocriptine.[139,140] In addition, an increased clearance of biologically active growth hormone has been reported,[138] possibly due to increased blood flow to liver and kidneys, sites of growth hormone metabolism. Thus, it is tempting to conclude that bromocriptine may indeed have a beneficial peripheral effect by impairing growth hormone bioactivity, unrelated to its direct effect on somatotropes. Further studies are required to clarify this possibility.

Predicting response to bromocriptine therapy. It has recently been shown that an initial suppression of growth hormone levels by 50% in response to the administration of 2.5 mg bromocriptine will reliably predict the long-term positive response to bromocriptine therapy. Furthermore, it would appear that TRH stimulation of growth hormone levels may predict a concordant suppressive effect of growth hormone by dopamine agonist therapy.[141] The presence of significant hyperprolactinemia has also been suggested as a positive predictor of growth hormone response to bromocriptine.[142]

Further studies are necessary to confirm the validity of these predictive tests.

Somatostatin analog. Because somatostatin is a physiologic inhibitor of growth hormone secretion, it was a natural candidate as a pharmacologic tool in treating acromegaly. Recently an octapeptide somatostatin analog—SMS 201-995, D-Phe-Cys-Phe-D-Trp-Lys-Thr-Cys-Thr (OH)—with high potency and prolonged inhibition of growth hormone secretion has been developed.[143] This analog, administered subcutaneously, has been successfully used to lower growth hormone levels in acromegaly. Indeed, SMS 201-995 has recently been found to provoke a prolonged decrease of growth hormone levels in seven of eight acromegalic patients tested. A short-lived suppression of insulin levels, however, with a concomitant rise in blood glucose levels was also noted.[144-146] Clinical trials currently under way will no doubt further evaluate the safety and efficacy of this promising new form of therapy.

Other medical treatments. Estrogens,[147] progesterone,[148] chlorpromazine[149] and cyproheptadine hydrochloride[150] have been used with varying degrees of success in the treatment of acromegaly.

Conclusion

Although recent studies have led to major advances in our understanding of the pathophysiology and etiology of acromegaly, successful therapy still remains elusive for many patients. The initial success of the transsphenoidal operation has been followed by less enthusiastic reports of long-term disease recurrence. Medical treatment, either primary or adjunctive, is likely to play an increasingly important therapeutic role during the next few years.

The significant progress made in unraveling the complexities of acromegaly in the past 100 years illustrates the fruitful application of advances in neuroendocrine physiology and cellular biochemistry to the understanding of this heterogeneous clinical disorder.

REFERENCES

1. Marie P: On two cases of acromegaly: Marked hypertrophy of the upper and lower limbs and the head. Rev Med 1886; 6:297-333

2. Benda C: Uber den normalen Bau and einige pathologische Veranderungen Hypophysis cerebri. Arch Anat Physiol Abt 1900; 314:373

3. Benda C: Beitrage zur normalen und pathologischen Histologie der menschlichen Hypophysis cerebri. Berliner Klin Wochenschr 1900; 37:1205-1210

4. Davidoff LM: Studies in acromegaly II—Historical note. Endocrinology 1926; 10:453-460

5. Evans HM, Long JA: The effect of the anterior lobe of the pituitary administered intraperitoneally upon growth, maturity and oestrus cycle of the rat. Anat Rec 1921; 21:62-63

6. Niall HD, Hogan ML, Tregear GW, et al: The chemistry of growth hormone and the lactogenic hormones. Recent Prog Horm Res 1973; 29:387-416

7. Frohman LA: Ectopic hormone production by tumors: Growth hormone releasing factor, *In* Muller EE, Macleod RM (Eds): Neuroendocrine Perspectives, Vol 3. Amsterdam, Elsevier, 1984, pp 201-224

8. Thorner MO, Rivier J, Spiess J, et al: Human pancreatic growth-hormone-releasing factor selectively stimulates growth-hormone secretion in man. Lancet 1983; 1:24-28

9. Brazeau P, Vale W, Burgus R, et al: Hypothalamic peptide that inhibits the secretion of immunoreactive pituitary growth hormone. Science 1973; 179:77-79

10. Thompson RG, Rodriguez A, Kowarski A, et al: Growth hormone: Metabolic clearance rates, integrated concentrations and production rates in normal adults and the effect of prednisone. J Clin Invest 1972; 51:3193-3199

11. Merimee TJ, Rabinowitz D, Fineberg SE: Arginine-initiated release of human growth hormone—Factors modifying the response in normal man. N Engl J Med 1969; 280:1434-1438

12. Wiedemann E, Schwartz E: Suppression of growth hormone dependent human serum sulfation factor by estrogen. J Clin Endocrinol Metab 1972 Jan; 34:51-58

13. Williams T, Maxon H, Thorner MO, et al: Blunted growth hormone (GH) response to GH-releasing hormone in hypothyroidism resolves in the euthyroid state. J Clin Endocrinol Metab 1985 Sep; 61:454-456

14. Salmon WD, Daughaday WH: A hormonally controlled serum factor which stimulates sulfate incorporation by cartilage in-vitro. J Lab Clin Invest 1957; 49:825-836

15. Schwander JC, Hauri C, Zapf J, et al: Synthesis and secretion of insulin-like growth factor and its binding protein by the perfused rat liver: Dependence on growth hormone status. Endocrinology 1983 Jul; 113:297-305

16. D'Ercole AJ, Stiles AD, Underwood LE: Tissue concentrations of somatomedin C: Further evidence for multiple sites of synthesis and paracrine or autocrine mechanisms of action. Proc Natl Acad Sci USA 1984 Feb; 81:935-939

17. Clemmons DR, Shaw DS: Purification and biological properties of fibroblast somatomedin. J Biol Chem 1986; 261:10283-10288

18. Bratusch-Marrain PR, Gasic S, Waldhäusl WK, et al: The effect of growth hormone on splanchnic glucose and substrate metabolism following oral glucose loading in healthy man. Diabetes 1984; 33:19-25

19. Fain JN: Studies on the role of RNA and protein synthesis in the lipolytic action of growth hormone in isolated fat cells, *In* Weber G (Ed): Advances in Enzyme Regulation, Vol 5. Oxford, Pergamon Press, 1967, pp 39-51

20. Berelowitz M, Szabo M, Frohman LA, et al: Somatomedin-C mediates growth hormone negative feedback by effects on both the hypothalamus and the pituitary. Science 1981 Jun; 212:1279-1281

21. Yamashita S, Weiss M, Melmed S: Insulin-like growth factor I regulates growth hormone secretion and messenger ribonucleic acid levels in human pituitary cells. J Clin Endocrinol Metab 1986; 63:730-735

22. Melmed S, Braunstein GD, Chang J, et al: Growth hormone and prolactin-secreting pituitary tumors. Ann Intern Med 1986; 105:238-253

23. Phifer RF, Spicer SS, Hennigar GG: Histochemical reactivity and staining properties of functionally defined cell types in the human adenohypophysis. Am J Pathol 1973; 73:569-587

24. Melmed S, Braunstein GD, Horvath E, et al: Pathophysiology of acromegaly. Endocr Rev 1983; 4:271-290

25. Horvath R, Kovacs K: Ultrastructural classification of pituitary adenomas. Can J Neurol Sci 1976; 3:9-21

26. Horvath E, Kovacs K: Pathology of the pituitary gland, *In* Ezrin C, Horvath E, Kaufman B, et al (Eds): Pituitary Diseases. Boca Raton, Fla, CRC Press, 1980, pp 1-83

27. Kovacs K, Horvath E, Pritzker KPH, et al: Pituitary growth hormone cell adenoma with cytoplasmic tubular aggregates in the capillary endothelium. Acta Neuropathol (Berl) 1977; 37:77-79

28. Kovacs K, Horvath E: Pituitary adenomas: Pathologic aspects, *In* Tolis G, Labrie F, Martin JB, et al (Eds): Clinical Neuroendocrinology—A Pathophysiological Approach. New York, Raven Press, 1979, pp 367-384

29. Kovacs K, Horvath E, Ryan N: Immunocytology of the human pituitary, *In* Delellis RA (Ed): Diagnostic Immunocytochemistry. New York, Masson, 1981, pp 17-35

30. Schelin U: Chromophobe and acidophil adenomas of the human pituitary gland—A light and electron microscopic study. Acta Pathol Microbiol Scand 1962; 158(suppl):1-80

31. Kinnman J: Acromegaly: An Ultrastructural Analysis of 51 Adenomas and a Clinical Study in 80 Patients Treated by Transanthrosphenoidal Operation. Stockholm, Norstadt & Soner, 1973, pp 1-226

32. Robert F: L'adénome hypophysaire dans l'acromégalie gigantisme—Etude macroscopique, histologique et ultrastructurale. Neurochirurgie 1973; 19(suppl):117-162

33. Schechter J: Electron microscopic studies of human pituitary tumors II—Acidophilic adenomas. Am J Anat 1973; 138:387-399

34. Landolt AM: Ultrastructure of human sella tumors—Correlations of clinical findings and morphology. Acta Neurochir (Wien) Suppl 1975; 22:1-167

35. Oliver L, Vila-Porcile E, Racadot O, et al: Ultrastructure of pituitary tumor cells: A critical study, *In* Tixier-Vidal A, Farquhar MG (Eds): The Anterior Pituitary. New York, Academic Press, 1975, pp 231-276

36. Halmi NS, Duello T: 'Acidophilic' pituitary tumor—A reappraisal with differential staining and immunocytochemical techniques. Arch Pathol Lab Med 1976; 100:346-351

37. Nieuwenhuyzen-Kruseman AC, Beta GTAM, Lindeman J, et al: Use of immunohistochemical and morphologic methods for the identification of human growth hormone-producing pituitary adenomas. Cancer 1976; 38:1163-1170

38. Halmi NS: Immunostaining of growth hormone cells and prolactin cells in paraffin-embedded and stored or previously stained material. J Histochem Cytochem 1978; 26:486-495

39. Robert F: Electron microscopy of human pituitary tumors, *In* Tindall GT, Collins WF (Eds): Clinical Management of Pituitary Disorders. New York, Raven Press, 1979, pp 113-131

40. Cardell RR Jr, Knightson RS: The cytology of a human pituitary tumor—An electron microscopic study. Trans Am Microsc Soc 1966; 85:58-78

41. Trouillas J, Girod C, Lheritier M, et al: Morphological and biochemical relationships in 31 human pituitary adenomas with acromegaly. Virchows Arch [A] 1980; 389:127-142

42. Ezrin C, Kovacs K, Horvath E: Pathology of the adenohypophysis, *In* Bloodworth JMB Jr (Ed): Endocrine Pathology. Baltimore, Williams & Wilkins, 1982, pp 101-132

43. Martinez AJ, Lee A, Moossy J, et al: Pituitary adenomas: Clinicopathological and immunohistochemical study. Ann Neurol 1980; 7:24-36

44. Guyda H, Robert F, Colle E, et al: Histologic, ultrastructural and hormonal characterization of a pituitary tumor secreting both hGH and prolactin. J Clin Endocrinol Metab 1973; 36:531-547

45. Zimmerman EA, Defendini R, Frantz AG: Prolactin and growth hormone in patients with pituitary adenomas—A correlative study of hormone in tumor and plasma by immunoperoxidase technique and radioimmunoassay. J Clin Endocrinol Metab 1974; 38:577-585

46. Corenblum B, Sirek AMT, Horvath E, et al: Human mixed somatotrophic and lactotrophic pituitary adenoma. J Clin Endocrinol Metab 1976; 42:857-863

47. Ezrin C, Kovacs K, Horvath E: Hyperprolactinemia—Morphologic and clinical considerations. Med Clin North Am 1978; 62:393-408

48. Kameya T, Tsumuraya M, Adachi I, et al: Ultrastructure, immunohistochemistry and hormone release of pituitary adenomas in relation to prolactin production. Virchows Arch [A] 1980; 387:31-46

49. Horvath E, Kovacs K, Singer W, et al: Acidophil stem cell adenoma of the human pituitary. Arch Pathol Lab Med 1977; 101:594-599

50. Horvath E, Kovacs K, Singer W, et al: Acidophil stem cell adenoma of the human pituitary—Clinico-pathological analysis of 15 cases. Cancer 1981; 47:761-771

51. Schleithauer BW: Surgical pathology of the pituitary and sellar region, *In* Laws ER Jr, Randall RV, Kern EB, et al (Eds): Management of Pituitary Adenomas and Related Lesions With Emphasis on Transsphenoidal Microsurgery. New York, Appleton-Century-Crofts, 1982, pp 129-218

52. Horvath E, Kovacs K, Killinger DW, et al: Mammosomatotroph cell adenoma of the human pituitary (Abstr). Proc Annu Meet Electron Microsc Soc Am 1980; 38:726

53. Lamberg BA, Ripatti J, Gordin A, et al: Chromophobe pituitary adenoma with acromegaly and TSH-induced hyperthyroidism associated with parathyroid adenoma: Acromegaly and parathyroid adenoma. Acta Endocrinol (Kobenh) 1969; 60:157-172

54. Kovacs K, Horvath E, Ezrin C, et al: Adenoma of the human pituitary producing growth hormone and thyrotropin—A histologic, immunocytologic and fine structural study. Virchows Arch [A] 1982; 394:59-68

55. Saeger W, Ludecke DK: Pituitary adenomas with hyperfunction of TSH—Frequency, histologic classification, immunocytochemistry and ultrastructure. Virchows Arch [A] 1982; 395:255-267

56. Erdheim J: Uber einen Hypophysentumor von ungewohnlichen Sitz. Beitr Pathol Anat Allg Pathol 1909; 46:233-240

57. Corenblum B, LeBlanc FE, Watanabe M: Acromegaly with an adenomatous pharyngeal pituitary. JAMA 1980; 243:1456-1457

58. Rasmussen P, Lindholm J: Ectopic pituitary adenomas. Clin Endocrinol 1979; 11:69-74

59. Sparagana M, Phillips G, Hoffman C, et al: Ectopic growth hormone syndrome associated with lung cancer. Metabolism 1971; 20:730-736

60. Kaganowicz A, Farkoub NH, Frantz AG, et al: Ectopic human growth hormone in ovaries and breast cancer. J Clin Endocrinol Metab 1979; 48:5-8

61. Melmed S, Ezrin C, Kovacs K, et al: Acromegaly due to secretion of growth hormone by an ectopic pancreatic islet-cell tumor. N Engl J Med 1985; 312:9-17

62. Asa SL, Bilbao JM, Kovacs K, et al: Hypothalamic neuronal hamartoma associated with pituitary growth hormone cell adenoma and acromegaly. Acta Neuropathol (Berl) 1980: 52:131-134

63. Rhodes RH, Dusseau JJ, Boyd AS Jr, et al: Intrasellar neural-adenohypophyseal choristoma—A morphological and immunocytochemical study. J Neuropathol Exp Neurol 1982; 41:267-280

64. Muller W: Uber das gemeinsame Vorkommen eines Hypophysenadenome mit einem Gangliocytom in zwei Faillen—Ein Beitrag zur Frage der Neurosekretion. Acta Neurochirurg 1956; 7:13-29

65. Thorner MO, Perryman RL, Cronin MJ, et al: Somatotroph hyperplasia—Successful treatment of acromegaly by removal of a pancreatic islet tumor secreting a growth hormone-releasing factor. J Clin Invest 1982; 70:965-977

66. Guillemin RR, Brazeau P, Böhlen P, et al: Growth hormone-releasing factor from a human pancreatic tumor that caused acromegaly. Science 1982; 218:585-587

67. Rivier J, Spiess J, Thorner M, et al: Characterization of a growth hormone-releasing factor from a human pancreatic islet tumor. Nature 1982; 300:276-278

68. Caplan RH, Koob L, Pagliara AS, et al: Cure of acromegaly by operative removal of an islet cell tumor of the pancreas. Am J Med 1978; 64:874-882

69. Frohman LA, Szabo M, Berelowitz M, et al: Partial purification and characterization of a peptide with GH releasing activity from extrapituitary tumors in patients with acromegaly. J Clin Invest 1980; 65:43-54

70. Dabek JT: Bronchial carcinoid tumor with acromegaly in two patients. J Clin Endocrinol Metab 1974; 38:329-333

71. Leveston SA, McKeel DW, Buckley PJ, et al: Acromegaly and Cushing's syndrome associated with a foreign carcinoid tumor. J Clin Endocrinol Metab 1981; 53:682-689

72. Saeed uz Zafar M, Mellinger RC, Fine G, et al: Acromegaly associated with a bronchial carcinoid tumor: Evidence for ectopic production of growth hormone-releasing activity. J Clin Endocrinol Metab 1979; 48:66-71

73. Shalet SM, Beardwell CG, MacFarlane LA, et al: Acromegaly due to production of a growth hormone releasing factor by a bronchial carcinoid tumor. Clin Endocrinol (Oxf) 1979; 10:61-67

74. Sonksen PH, Ayres AB, Braimsbridge M, et al: Acromegaly caused by pulmonary carcinoid tumors. Clin Endocrinol (Oxf) 1976; 5:503-513

75. Velasco ME, Sindely SO, Roessmann U: Reticulum stain for frozen section diagnosis of pituitary adenomas—Technical note. J Neurosurg 1977; 46:548-550

76. Thorner MO, Frohman LA, Leong DA, et al: Extrahypothalamic growth hormone-releasing factor (GRF) secretion is a rare cause of acromegaly: Plasma GRF levels in 177 acromegalic patients. J Clin Endocrinol Metab 1984; 59:846-849

77. Ashcraft MW, Hartzband PI, Van Herle AJ, et al: A unique growth factor in patients with acromegaloidism. J Clin Endocrinol Metab 1983; 57:272-276

78. Jadresic A, Banks LM, Child DF, et al: The acromegaly syndrome—Relation between clinical features, growth hormone values and radiological characteristics of the pituitary tumors. Q J Med 1982; 202:119-204

79. Reichlin S: Acromegaly. Medical Grand Rounds 1982; 1:9-24

80. Ferguson JK, Donald RA, Weston TS, et al: Skin thickness in patients with acromegaly and Cushing's syndrome and response to treatment. Clin Endocrinol (Oxf) 1983; 18:347-353

81. Kho KM, Wright AD, Doyle FH: Heel pad thickness in acromegaly. Br J Radiol 1970; 43:119-125

82. Klein I, Parveen G, Gavaler JS, et al: Colonic polyps in patients with acromegaly. Ann Intern Med 1982; 97:27-30

83. Ituarte EA, Petrini J, Hershman JM: Acromegaly and colon cancer. Ann Intern Med 1984; 101:627-628

84. De Pablo F, Eastman RC, Roth J, et al: Plasma prolactin in acromegaly before and after treatment. J Clin Endocrinol Metab 1981; 53:344-352

85. Faglia G, Arosio M, Ambrosi B: Recent advances in diagnosis and treatment of acromegaly, *In* Imura H (Ed): The Pituitary Gland. New York, Raven Press, 1985, pp 363-404

86. Lamburg BA, Pelkonen R, Ano A, et al: Thyroid function in acromegaly before and after transsphenoidal hypophysectomy followed by cryoapplication. Acta Endocrinol (Copenh) 1976; 82:254-266

87. Mukhtar E, Alexander L, Wilkinson R, et al: Thyroid function in acromegaly. Lancet 1971; 2:279-283

88. Lund B, Eskildsen PC, Lund B, et al: Calcium and vitamin D metabolism in acromegaly. Acta Endocrinol (Copenh) 1981; 96:444-450

89. Ballard HS, Frame B, Hartsock RD: Familial multiple endocrine adenoma-peptic ulcer complex. Medicine (Baltimore) 1964; 43:481-516

90. Bijlsma JWJ, Nortier JWR, Dwursma SA, et al: Changes in bone metabolism during treatment of acromegaly. Acta Endocrinol (Copenh) 1983; 104:153-159

91. Lawrence AM, Goldfine ID, Kirsteins L: Growth hormone dynamics in acromegaly. J Clin Endocrinol Metab 1970; 31:239-247

92. Wass JAH: Acromegaly, *In* Belchetz PE (Ed): Management of Pituitary Disease. New York, Wiley Medicine, 1984, pp 123-140

93. Cryer PE, Daughaday WH: Regulation of growth hormone secretion in acromegaly. J Clin Endocrinol Metab 1969; 29:386-393

94. Cryer PE, Daughaday WH: Growth hormone, *In* Martini L, Besser GM (Eds): Clinical Neuroendocrinology. New York, Academic Press, 1977, pp 243-277

95. Faglia G, Arosio M, Ambrosi B, et al: Hypothalamic-pituitary function studies in the diagnosis and follow-up of acromegaly, *In* Derome PJ, Jedynak CP, Peillon F (Eds): Pituitary Adenomas. Paris, Asclepios Publishing, 1980, pp 131-139

96. Tolis G, Kootsilieris M, Bertrand G: Endocrine diagnosis of growth hormone-secreting pituitary tumors, *In* Black PM, Zervas NT, Ridgway EC, et al (Eds): Secretory Tumors of the Pituitary Gland—Progress in Endocrine Research and Therapy, Vol 1. New York, Raven Press, 1984, pp 145-154

97. Irie M, Tsushima T: Increase of serum growth hormone concentration following thyrotropin-releasing hormone injection in patients with acromegaly or gigantism. J Clin Endocrinol Metab 1972; 35:97-100

98. Zapf J, Waldvogel M, Froesch ER: Binding of non-suppressible insulin-like activity to human serum—Evidence for a carrier protein. Arch Biochem Biophys 1975; 168:638-645

99. Hintz RL, Liu F: Demonstration of specific plasma protein binding sites for somatomedin. J Clin Endocrinol Metab 1977; 45:988-995

100. Clemmons DR, Van Wyk JJ, Ridgway EC, et al: Evaluation of acromegaly by radioimmunoassay of somatomedin C. N Engl J Med 1979; 301:1138-1142

101. Rieu M, Girard F, Bricaire H, et al: The importance of insulin-like growth factor (somatomedin) measurements in the diagnosis and surveillance of acromegaly. J Clin Endocrinol Metab 1982; 55:147-153

102. Clemmons DR, Van Wyk JJ: Factors controlling blood concentration of somatomedin C. Clin Endocrinol Metab 1984; 13:113-143

103. Unterman TG, Vazquez RM, Slas AJ, et al: Nutrition and somatomedin—XIII. Usefulness of somatomedin C in nutritional assessment. Am J Med 1985; 78:228-234

104. Stonesifer LD, Jordan RM, Kohler PO: Somatomedin C in treated acromegaly: Poor correlation with growth hormone and clinical response. J Clin Endocrinol Metab 1981; 53:931-934

105. Wass JAM, Clemmons DR, Underwood LE, et al: Changes in circulating somatomedin-C levels in bromocriptine-treated acromegaly. Clin Endocrinol (Oxf) 1982; 17:369-377

106. Wolpert SM: The radiology of pituitary adenomas—An update, *In* Post KD, Jackson IMD, Reichlin S (Eds): The Pituitary Adenoma. New York & London, Plenum Medical Books, 1980, pp 287-320

107. Bernasconi V, Travaglini P, Gaini SM, et al: High resolution CT in pituitary hypersecretion syndromes, *In* Camanni F, Molinatti GM, Muller EE (Eds): Pituitary Hyperfunction Physiopathology and Clinical Aspects—Vol 10, Serono. New York, Raven Press, 1984, pp 369-383

108. Bilaniuk LT, Zimmerman RA, Wherli FW, et al: Magnetic resonance imaging of pituitary lesions using 1.0 to 1.5 T field strength. Radiology 1984; 153:415-418

109. Quabbe HJ: Treatment of acromegaly by transsphenoidal operation—90-Yttrium implantation and bromocriptine: Results in 230 patients. Clin Endocrinol (Oxf) 1982; 16:107-120

110. Jaquet P, Guibout M, Jaquet C, et al: Circadian regulation of growth hormone secretion after treatment of acromegaly. J Clin Endocrinol Metab 1980; 50:322-328

111. Arafah BM, Brodkeys JS, Kaufman B, et al: Transsphenoidal microsurgery in the treatment of acromegaly and gigantism. J Clin Endocrinol Metab 1980; 50:578-585

112. Hoyte KM, Martin JB: Recovery from paradoxical growth hormone responses in acromegaly after transsphenoidal selective adenomectomy. J Clin Endocrinol Metab 1975; 41:656-659

113. Pearson DH, Arafah B, Brodley J: Management of acromegaly. Ann Intern Med 1981; 95:225-227

114. Arosio M, Giovanelli MA, Riva E, et al: Clinical use of pre- and post-surgical evaluation of abnormal GH responses in acromegaly. J Neurosurg 1983; 59:402-408

115. Eastman RC, Gordon P, Roth J: Conventional supervoltage irradiation is an effective treatment for acromegaly. J Clin Endocrinol Metab 1979; 48:931-940

116. Lamberg BA, Kivikangas V, Vartianen J, et al: Conventional pituitary irradiation in acromegaly. Acta Endocrinol (Copenh) 1976; 82:267-281

117. Lawrence AM, Pinsky SM, Goldfine ID: Conventional radiation therapy in acromegaly—A review and reassessment. Arch Intern Med 1971; 128:369-377

118. Kjellberg RN, Kliman B, Swisher BJ: Radiosurgery for pituitary adenoma with bragg peak proton beam, *In* Derome PJ, Jedynak CP, Peillon F (Eds): Pituitary Adenomas. Paris, Asclepios Publishing, 1980, pp 209-217

119. Cushing H: Partial hypophysectomy for acromegaly: With remarks on the function of the hypophysis. Ann Surg 1909; 1:1002-1018

120. Belopavlovic M, Buchthal A, Beks JW: Transfrontal pituitary surgery: Clinical results, intraoperative management and postoperative monitoring. Acta Neurochir (Wien) 1982; 64:9-18

121. Post KD: Transfrontal surgery for pituitary tumors, *In* Post KD, Jackson IMD, Reichlin S (Eds): The Pituitary Adenoma. New York, Plenum Medical Books, 1980, pp 401-415

122. Laws ER, Randall RV, Abboud CF: Surgical treatment of acromegaly: Results in 140 patients, *In* Givens JR (Ed): Hormone Secretory Pituitary Tumors. Chicago, London, Year Book Medical Publishing, 1982, pp 225-228

123. Hang HU, Wilson CB, Tyrrel JB: Transsphenoidal microhypophysectomy in acromegaly. J Neurosurg 1977; 47:840-852

124. Serri O, Somma M, Comtois R, et al: Acromegaly: Biochemical assessment of cure after long-term follow-up of transsphenoidal selective adenomectomy. J Clin Endocrinol Metab 1985; 61:185-189

125. Balagura S, Derome P, Guiot G: Acromegaly: Analysis of 132 cases treated surgically. Neurosurgery 1981; 8:413-416

126. Baskin DS, Boggan UE, Wilson CB: Transsphenoidal microsurgical removal of growth hormone-secreting pituitary adenomas. J Neurosurg 1982; 56:634-641

127. Schuster LD, Bantle JP, Oppenheimer JH, et al: Acromegaly: Reassessment of the long-term therapeutic effectiveness of transsphenoidal pituitary surgery. Ann Intern Med 1981; 95:172-174

128. Clayton RN, Vrionides Y, Lynch SS, et al: Response of acromegaly to long-term bromocriptine therapy: A biochemical and clinical assessment. Acta Endocrinol (Copenh) 1978; 89:469-482

129. Cassar J, Mashiter K, Joplin GF: Bromocriptine treatment of acromegaly. Metabolism 1977; 26:539-547

130. Chiodini PG, Liuzzi A, Botalla L, et al: Stable reduction of plasma growth hormone (hGH) levels during chronic administration of 2-Br-ergocryptine (CB-154) in acromegalic patients. J Clin Endocrinol Metab 1975; 40:705-708

131. Roelfsema F, Goslings BM, Frolich M, et al: The influence of bromocriptine on serum levels of growth hormone and other pituitary hormones and its metabolic effects in active acromegaly. Clin Endocrinol (Oxf) 1979; 11:235-244

132. Sachdev Y, Garg VK, Gopal K: Bromocriptine therapy in acromegaly—A long term review of 35 cases. Postgrad Med J 1981; 57:210-216

133. Thorner MO, Fluckiger F, Calne DB: Bromocriptine therapy for acromegaly, chap 4, Bromocriptine: A Clinical and Pharmacological Review. New York, Raven Press, 1980, pp 100-123

134. Wass JAM, Moult PJA, Thorner MO, et al: Reduction in pituitary tumor size in patients with prolactinomas and acromegaly treated with bromocriptine with or without radiotherapy. Lancet 1979; 2:66-69

135. Spark RF, Baker R, Bienfang DC, et al: Bromocriptine reduces pituitary tumor size and hypersecretion—Requiem for pituitary surgery? JAMA 1982; 247:311-316

136. Nortier JWR, Croughs RJM, Thijssen JHH, et al: Bromocriptine therapy in

acromegaly: Effects on plasma GH levels, somatomedin-C levels and clinical activity. Clin Endocrinol (Oxf) 1985; 22:209-217

137. Wass JAH, Thorner MO, Morris DV, et al: Long term treatment of acromegaly with bromocriptine. Br Med J 1977; 1:875-878

138. Maneschi F: Reappraisal of bromocriptine treatment for acromegaly. Horm Res 1980; 12:191-205

139. Hizuka N, Hendricks CM, Roth J, et al: Failure of bromocriptine to alter the qualitative characteristics of human growth hormone in acromegaly. Metabolism 1984; 33:582-584

140. Carlson HE, Levin SR, Braunstein GD, et al: Effect of bromocriptine on serum hormones in acromegaly. Horm Res 1984; 19:142-152

141. Nortier JWR, Croughs RJM, Donker GH, et al: Changes in plasma GH levels and clinical activity during bromocriptine therapy in acromegaly—The value of predictive tests. Acta Endocrinol (Copenh) 1984; 106:175-183

142. Lamberts SW, Liuzzi A, Chiodini PG, et al: The value of plasma prolactin levels in the prediction of the responsiveness of growth hormone secretion to bromocriptine and TRH in acromegaly. Eur J Clin Invest 1982; 12:151-155

143. Bauer W, Briner U, Doepfner W, et al: SMS 201-955: A very potent and selective octapeptide analogue of somatostatin with prolonged action. Life Sci 1982; 31:1133-1140

144. Lamberts SWJ, Oosterom R, Neufeld M, et al: The somatostatin analog SMS 201-995 induces long-acting inhibition of growth hormone secretion without rebound hypersecretion in acromegalic patients. J Clin Endocrinol Metab 1985; 60:1161-1165

145. Daughaday WH: A new treatment for an old disease (Editorial). N Engl J Med 1985; 313:1604-1605

146. Lamberts SWJ, Uitterlinden P, Verschoor L, et al: Long-term treatment of acromegaly with the somatostatin analogue SMS 201-995. N Engl J Med 1985; 313:1576-1580

147. Schwartz E, Echemendia E, Schiffer M, et al: Mechanism of estrogenic action in acromegaly. J Clin Invest 1969; 48:260-270

148. Lawrence AM, Kirsteins L: Progestins in the medical management of active acromegaly. J Clin Endocrinol Metab 1970; 30:646-652

149. Dimond RC, Brammer SR, Atkinson RL, et al: Chlorpromazine treatment and growth hormone secreting responses in acromegaly. J Clin Endocrinol Metab 1973; 36:1189-1195

150. Vigneri R, Goldfine ID: Pharmacologic therapy of patients with pituitary tumors secreting prolactin, growth hormone and adrenocorticotrophin. Adv Intern Med 1980; 25:69-89

Medical Practice Question

EDITOR'S NOTE: *From time to time medical practice questions from organizations with a legitimate interest in the information are referred to the Scientific Board by the Quality Care Review Commission of the California Medical Association. The opinions offered are based on training, experience and literature reviewed by specialists. These opinions are, however, informational only and should not be interpreted as directives, instructions or policy statements.*

Gastric Balloon for the Treatment of Obesity

QUESTION:

Is the gastric balloon, a soft, plastic inflatable device placed endoscopically in the stomach in order to control appetite, considered accepted medical practice to aid weight reduction in obese patients?

OPINION:

In the opinion of the Scientific Advisory Panels on General Surgery and Internal Medicine, use of the gastric balloon for the treatment of obesity should be considered investigational until controlled clinical studies, some of which are now in progress, define the full extent of potential complications and document its safety and long-term effectiveness in maintaining weight loss. The gastric balloon is a soft, plastic device that is placed in a patient's stomach endoscopically. After inflation, it is left to float free in the upper stomach for several months. The balloon is intended to be a temporary treatment, used with diet therapy and behavior modification for those obese patients who have failed to lose weight with these conventional methods alone.

In the short term, the gastric balloon has been shown to curb appetite and aid in weight reduction, with a minimum of serious complications. In fact, the Food and Drug Administration has approved one device based on this evidence. However, the advisory panels consider widespread use of the gastric balloon premature, until more clinical data are accumulated and the long-term results of weight maintenance following removal of the balloon are clearly established.